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SIR—Recently, a rare functional variant, I425V, in the serotonin transporter gene (*SLC6A4*) has been reported to be associated with a complex neuropsychiatric phenotype that includes obsessive-compulsive disorder (OCD), alcohol abuse/dependence, anorexia nervosa, and pervasive developmental disorder (PDD).[1] Our study, performed in a large population of patients with these disorders, confirms the occurrence and the segregation of V425 in OCD.

The neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) has been implicated in numerous psychiatric disorders, mostly because of the efficacy of serotonin reuptake inhibitors (SRIs). Among the polymorphisms identified in *SLC6A4*, three have been shown to be functional. The rare I425V variation, located in exon 9, increases the transport activity of the protein[2], whereas the two more frequent polymorphisms, 5-HTTLPR located in the 5'-UTR of the gene, and STin2 located in intron 2, modify the transcriptional activity of the gene[3,4]. Despite a large number of studies, the functional implications of the two frequent *SLC6A4* polymorphisms in psychiatric disorders are still a matter of debate. In the present study, we sought to further explore the influence of the rare but clearly functional I425V variant in a large sample of patients with OCD and other psychiatric conditions previously reported in the two families carrying I425V, i.e., PDD, anorexia nervosa, and alcohol abuse/dependence.

To be included in the study, patients had to meet the DSM-IV criteria for OCD, anorexia nervosa, alcohol abuse/dependence, or PDD. The diagnosis of PDD was confirmed using the Autism Diagnostic Interview-Revised.[5] For the other disorders, lifetime psychiatric evaluation was carried out using the Diagnostic Interview for Genetic Studies (DIGS)[6] for adult patients, or the Kiddie Schedule for Affective Disorders and Schizophrenia for children.[7] Healthy controls were included after being interviewed with the DIGS and the Family Interview for Genetic Studies[8] to confirm the absence of both personal and family history of major psychiatric disorders. The local Research Ethics Boards reviewed and approved the study.

The V425 was found in 3/254 probands with OCD, 1/284 with PDD, 1/124 with anorexia nervosa, in 1/285 healthy controls, but not in alcohol abusers/dependents (0/128) (Table 1). In OCD family 1, V425 was transmitted by the father who also had a lifetime history of OCD and single phobia. The paternal grandfather was alcoholic and tobacco dependant. No genotypic information was available for the paternal grandparents since the grandfather died of throat cancer and the grandmother of breast cancer. In OCD family 2, the mother and two siblings of the proband had committed suicide and the father was also dead, so no genotypic information was available for these individuals. OCD case 1 had only one brother, who committed suicide some years ago, so no genotypic information was available for him. No other clinical data were available concerning the first-degree relatives of OCD case 1. In PDD family 1, V425 was transmitted by the father and was present in the proband and two brothers. The father and one of the brothers carrying the V425 were both alcohol dependent. However, the youngest brother (19 years old), also carrying the V425 variant, did not suffer from alcoholism or any other psychiatric disorder at the time of evaluation.

Our results are in accordance with those previously reported by Ozaki et al[1] on four points. First,

we report a possibly higher occurrence of the V425 variant in OCD compared to controls. Although the variant is rare, the combined results of the two studies indicate a significantly higher frequency of V425 in OCD compared to controls[1,9] (5/457 *vs*. 2/884, Fisher exact test, $P= 0.02$). Second, despite the limited clinical and genotypic information on the families carrying the V425 variant, our results suggest a possible co-segregation between the V425 and neuropsychiatric phenotypes, specifically in OCD. Third, Ozaki et al. hypothesized that the V425 variant may confer treatment-resistance to SRIs. This was indirectly supported by our findings since all OCD probands carrying the V425 variant in our study were considered resistant to SRIs, i.e., the severity of their obsessive and compulsive symptoms decreased less than 25% with multiple trials of a high dose of SRIs and a good compliance. Specifically, the three probands with OCD carrying the variant showed poor or no response to multiple trials of SRIs at adequate doses over several years. Fourth, the analysis of the two additional polymorphisms of the *SCL6A4* gene indicated that the V425 polymorphism might be associated with the L allele of 5-HTTLPR. However, our results do not confirm the hypothesis of a combined gain of function effect of both V425 and L/L genotype as a genetic risk for OCD, since this combined genotype was not present in all affected patients and, by contrast, was present in the control subject carrying the V425 variant.

In conclusion, our results are similar to those of the original report by Ozaki et al. and, therefore, lend support for a role of *SLC6A4* V425 in the susceptibility to complex neuropsychiatric phenotypes. However, due to its global low frequency and to the fact that it was detected in a few controls, the role of V425 remains uncertain and should be interpreted with caution. We encourage other investigators, especially in the field of OCD, to screen for V425 in their samples. Indeed, the replication of these findings could ultimately implicate *SLC6A4* as a true susceptibility gene to complex neuropsychiatric disorders, and consequently shed further light on the results obtained with the more frequent polymorphisms.

References

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Table 1 SCL6A4 genotypes and clinical features of the subjects included in the study

	SCL6A4 genotypes [a]			*Clinical features*	
	5'-UTR 5-HTTLPR	*Intron 2 VNTR STin2*	*Exon 9 I425V*	*Lifetime axis I disorders*	*Response to SRIs*[b]
OCD (n=254)					
OCD family 1					
Father	L/S	12/12	Ile/Val	OCD, simple phobia	Spontaneous remission
Mother	L/S	10/12	Ile/Ile	No disorder	
Proband (male, 29 years)	L/L	10/12	Ile/Val	OCD, panic disorder, simple phobia, dysthymia	Resistance to SRIs – never achieved clinical remission
Sister	L/L	10/12	Ile/Ile	no disorder	
OCD family 2					
Proband (female, 61years)	L/L	10/12	Ile/Val	OCD, dysthymia	Resistance to SRIs— never achieved clinical remission
Daughter	—	—	Ile/Ile	No disorder	
OCD case 1 (female, 33 years)	L/S	12/12	Ile/Val	OCD, major depressive disorder	Resistance to SRIs— never achieved clinical remission
Pervasive developmental disorder (n=284)					
PDD family 1					
Father	L/L	10/12	Ile/Val	Alcohol-dependence, depression	
Mother	L/S	12/12	Ile/Ile	No disorder	
Proband (male, 29 years)	L/S	12/12	Ile/Val	Autism, severe mental retardation, echolalic speech	
Sister	L/S	10/12	Ile/Ile	No disorder	
Brother	L/S	10/12	Ile/Ile	No disorder	
Brother (22 years)	L/S	12/12	Ile/Val	Drug and alcohol-dependence, depression, ADHD	
Brother (19 years)	L/S	12/12	Ile/Val	No disorder	
Anorexia nervosa (n=124)					
Anorexia nervosa family 1					
Father	L/S	12/12	Ile/Val	No clinical evaluation	
Mother	L/S	12/12	Ile/Ile	No clinical evaluation	
Proband (female, 19 years)	L/S	12/12	Ile/Val	Anorexia nervosa	
Alcohol–dependence (n=128)					
None carried the mutation					
Healthy controls (n=285)					
T115 (male, 33 years)	L/L	10/12	Ile/Val	No disorder	

ADHD, attention deficit hyperactivity disorder; OCD, obsessive-compulsive disorder; PDD, pervasive developmental disorder; SRIs, serotonin reuptake inhibitors.

[a] The polymorphisms 5-HTTLPR and STin2 were genotyped using methods described previously.[10] Genotyping of the I425V variation was performed by direct sequencing.

[b] Benefits in symptom severity were less than 25% with multiple trials of a high dose of SRIs and a good compliance.